1134-156 Effects of Antidepressant Medication on Mortality in Patients With Congestive Heart Failure

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Major Depressive Disorder (MDD) is a common entity in patients with cardiovascular (CAD) disease. Studies have previously demonstrated that MDD is present in 20%-45% of CAD patients. Rates of depressive disorders following myocardial infarction (MI) are especially high, with a depressive episode in 50% of patients immediately following MI, and more than 70% at one year after MI. Congestive heart failure (CHF) due to ischemia occurs in many of these patients. Despite numerous studies in this population, few have focused on the prevalence of depression and its prognostic effect in patients with CHF. Recently Jiang et al. published results demonstrating that overall mortality in patients with co-morbid CHF and depression was increased at 3 months and 1 year compared to patients with CHF who were not depressed. MDD with CHF was found to be an independent risk factor for increased mortality. In the current work we have confirmed these findings, with increased mortality in patients with CHF and co-morbid depression by Beck Depression Inventory (BDI=10) in a group of 674 patients with ejection fraction less than or equal to 35%. Patients who were not depressed at baseline but had CHF had a mortality rate of 12.12%. Those patients at baseline on antidepressant medication, and in all likelihood responsive to medication, had a mortality rate of 14.14%. While patients who at baseline were depressed and treated with medication, suffered increased mortality over controls at 22.52%. In CHF patients with major depression whose depressive symptoms did not respond to medication effect had an even higher rate of mortality at 38.60% (p-value=0.5). This data suggests that patients with co-morbid CHF and depression and who remain non-responders despite medication have higher rates of mortality over those without depression, or those patients responsive to medication. This work proposes that the effect of adequately treating depression in patients with CHF may reduce mortality, and if the CHF/depressed patient remains non-responsive to medication, mortality may be significantly higher than that either depressed-responsive/CHF or non-depressed patients with CHF.

1134-157 Endothelin Antagonism With Bosentan, a Dual Receptor Blocker, Normalizes Dysregulated Transforming Growth Factor Beta Signaling Pathways in Rats With Chronic Heart Failure

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Background: We have previously shown that dysregulation of the TGF beta signaling pathway is correlated with adverse ventricular remodeling in CHF. Endothelin (ET) also plays a central role in ventricular remodeling and many of its actions are mediated by TGF beta. Therefore, we hypothesized that the beneficial effects of ET antagonism with bosentan on ventricular remodeling may be mediated by improvements in the TGF beta signaling pathway.
Methods: Adult male Sprague-Dawley rats (270-300g) underwent coronary artery ligation (CAL) or sham operation (Sham group) followed by conscious echocardiography on day 5-7 after surgery. CAL rats with ejection fraction 3 in all groups).
Results: Baseline data (EF, body weight) showed no differences between the treatment groups. In myocytes from CHF rats, bosentan tended to increase inhibitory Smad6 by 51% (p=0.13), with no effect on the positive effectors, Smad3 or Smad4. In fibroblasts from CHF rats, bosentan decreased Smad4 and SARA (Smad anchor for receptor activation; p=0.018) to normal and significantly increased Smad6 (97%; p=0.026). The improvements in fibroblast Smad6 concentrations directly correlated with attenuation of ventricular dilation by bosentan, as measured by LV volume at 20 mmHg distending pressure (p<0.01; r=0.69).
Conclusion: These data confirm our earlier findings of TGF beta signaling pathway dysregulation in CHF and demonstrate that chronic ET blockade with bosentan results in normalization of these pathways. Inhibition of the TGF beta pathway was directly correlated to the beneficial effects of bosentan on ventricular remodeling. These findings suggest that the TGF beta pathway may mediate the adverse effects of endothelin in CHF and that this pathway may be an important therapeutic target in CHF.

1134-158 Long-Term Carvedilol Treatment in Idiopathic Dilated Cardiomyopathy: Biological Effects Beyond Pharmacological Activity

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Background. Despite the established effects of carvedilol on morbility and mortality in heart failure (HF), the mechanisms of its clinical efficacy are still poorly understood. We conducted a multicenter, double-blind, randomized, placebo-controlled trial in HF patients with idiopathic dilated cardiomyopathy to assess the effects of carvedilol (C) on submaximal exercise tolerance during long-term pharmacological treatment and after withdrawal. Methods and Results. 99 patients with HF due to documented idiopathic dilated cardiomyopathy and an ejection fraction <=0.35 underwent a 2-week open-label challenge with C; 84 of them (mean age 54±10 years, 64 males) were randomized to chronic treatment with C (n=45), titrated up to 25 mg bid (mean final dose 23.1±4.8 bid) or placebo (P), (n=39) on top of ACE-inhibitors and form the intention-to-treat sample. After 6-month treatment, Minnesota Living with Heart Failure (MLWHFQ) questionnaire, echo ejection fraction and submaximal exercise stress test were compared to baseline; exercise tolerance was again assessed after 5.4±5 days wash-out. Improvement in submaximal exercise tolerance, defined as a 20% increase and an absolute increase of at least 60 sec in exercise duration after 6-month treatment vs baseline, occurred in 51% of C and 23% of P (p=0.01). Changes in exercise duration were 103±257 sec in C vs -19±160 sec in P during chronic treatment and 123±306 sec in C vs -2±178 sec in P after wash-out (p=0.014 for treatment effect). Peak exercise systolic blood pressure and heart rate did not change in both groups. MLWHFQ total score decreased by -5±12 points in C vs -1±9 points in P (p=0.01); MLWHFQ physical dimension score decreased by -2±5 points in C vs 0±4 points in P (p=0.03). Ejection fraction increased by 6.1±8.9 units in C vs 3.2±5.2 units in P (p=0.08). Conclusions. In idiopathic dilated cardiomyopathy, C determines during long-term treatment, beyond an improvement in symptoms and systolic function, a significant increase in submaximal exercise tolerance, that is maintained even after pharmacological wash-out. The sustained effects after drug withdrawal indicate that C-induced benefits in HF are biologically-mediated.

1134-159 Effect of Valsartan on Time-Adjusted and Hospitalization Frequency Rate in the Valsartan Heart Failure Trial

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Background: In the Valsartan Heart Failure Trial (Val-HeFT), risk for time to first heart failure (HF) hospitalization adjudicated by the Endpoint Committee was reduced by 27.5% with valsartan versus placebo in 5010 patients with NYHA class II-IV HF receiving prescribed therapy. HF and cardiovascular (CV) hospitalizations (investigator-classified) were markedly reduced (HF 22.4%, CV 15.4%) by valsartan versus placebo. Significant reductions were also seen in subgroups defined by background therapy (angiotensin converting enzyme inhibitor = ACE, beta blocker = BB), principally in patients not on BB. However, total hospitalization data should be adjusted for time at risk to account for differential mortality.
Methods: For purposes of this analysis, cause of hospital admissions was investigator-classified.
Results: In Val-HeFT, a reduction in HF and CV hospitalization rate with valsartan is observed in all subgroups except those treated with both ACE and BB. The number of patients hospitalized also was reduced by valsartan compared to placebo, particularly those hospitalized more than once (1: HF 8.7%, CV 7.5%; 2 or more: HF 20.7%, CV 11.8%).
Conclusion: The beneficial effects on the overall HF and CV hospitalization rates in Val-HeFT confirm the adjudicated first HF hospitalization endpoint. Reduction of hospitalization rates is most strongly noted in patients with recurrent hospitalizations.

HF Hospitalizations

	Total Number		Per patient-year		
Subgroup	Valsartan	Placebo	Valsartan	Placebo	p-value
All	923	1189	0.30	0.36	0.001
BB=yes	266	298	0.25	0.24	0.686
BB=no	657	891	0.32	0.43	<0.001
ACE=yes	872	1072	0.31	0.35	0.011
ACE=no	51	117	0.18	0.51	0.007
BB(y)+ACE(y)	254	269	0.27	0.22	0.953
BB(y)+ACE(n)	12	29	0.11	0.45	0.102
BB(n)+ACE(y)	618	803	0.33	0.42	0.002
BB(n)+ACE(n)	39	88	0.22	0.55	0.032

1134-160 Early Detection of Regional Myocardial Dysfunction by Strain Doppler Echocardiography in Patients With Primary Amyloidosis

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Background: Tissue Doppler imaging (TDI) shows a reduced longitudinal myocardial velocity gradient between the base and mid-ventricle in amyloidosis with heart failure (CHF). We sought to determine the precise site of the regional contractile abnormality using strain rate imaging (SRI).
Methods: 88 biopsy-proven patients with AL amyloidosis underwent TDI and SRI. 54 had heart involvement, of whom 26 had CHF. 28 had cardiac involvement but no CHF and 34 had non-cardiac amyloid (controls). Sample volumes were placed on basal, mid, and apical ventricle at the septum, lateral, and inferior walls in the apical views. Peak TDI and SRI were measured in systole (S) and early (E) diastole.
Results: Using TDI, differences in systolic function were only apparent between the CHF and the other 2 groups, but TDI could not distinguish the controls from "no-CHF". In contrast, peak SRI-S distinguished "no-CHF" from controls. The difference was most apparent at the mid-ventricle (table), whereas basal peak SRI-S did not differ between "no-CHF" and controls. Similarly, peak SRI-E in the "no-CHF" showed a significantly lower value than in the controls at the mid-ventricle but not the base, whereas TDI-E did not show any difference between the "no-CHF" and controls.
Conclusion: In cardiac amyloid, systolic and diastolic myocardial dysfunction show regional differences. Dysfunction is seen prominently and earliest in the mid-ventricular walls. The abnormalities, while poorly detected by TDI, can be demonstrated by SRI.